

Lixisenatide: evidence for its potential use in the treatment of type 2 diabetes

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Abstract: Lixisenatide is a once-daily glucagon-like peptide 1 (GLP-1) receptor agonist mimicking several favorable actions of endogenous GLP-1 that result in improved glycemic control with little or no hypoglycemia and weight loss. Phase II trials have shown that lixisenatide 20 µg once daily restores first-phase insulin release in patients with type 2 diabetes and improves the second-phase insulin response. Administered once or twice daily for 4 weeks, it significantly reduced postprandial and fasting blood glucose levels, and glycosylated hemoglobin (HbA_{1c}). The efficacy and safety of lixisenatide once daily is being assessed in the GETGOAL Phase III clinical trial program. Results have shown beneficial effects on HbA_{1c} compared with placebo in combination with commonly used antidiabetes agents, with no increased risk of hypoglycemia and with beneficial weight reduction. Adverse effects were similar to those observed for available GLP-1 receptor agonists, the most frequent being gastrointestinal. Both GLP-1 receptor agonists and long-acting insulin analogs have demonstrated protective effects on beta cells in preclinical studies. This, along with the pronounced effect of lixisenatide on postprandial plasma glucose, provides a rationale for combining it with long-acting basal insulin analogs, in the hope that the additive effects on glycemic control combined with a potential benefit on islet cells may lead to a new treatment approach to control blood glucose better and prevent long-term complications in patients with type 2 diabetes.

Keywords: GLP-1 receptor agonist, combination therapy, GETGOAL program, insulin, lixisenatide, postprandial plasma glucose, type 2 diabetes

Core Evidence clinical impact summary for lixisenatide in type 2 diabetes

Outcome measure	Evidence	Implications
Disease-oriented evidence	Demonstrates all the beneficial effects associated with glucagon-like peptide 1 receptor agonists: improved glycemic control, increased meal-related and glucose-stimulated insulin secretion, suppression of glucagon, weight loss, delayed gastric emptying, appetite suppression, and enhanced beta cell function	Provides another therapeutic choice for a large patient population
	Lixisenatide has a pronounced effect on postprandial plasma glucose levels	Provides a rationale for combining with long-acting insulin analogs for additive effects on glycemic control

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<i>(Continued)</i>		
Outcome measure	Evidence	Implications
Patient-oriented evidence		
Hypoglycemia	Low risk of hypoglycemia in combination with insulin	If approved, lixisenatide may offer an alternative in patients in whom hypoglycemia must be avoided or weight loss is important
Gastrointestinal adverse events	Nausea is the most frequent adverse event similar to other glucagon-like peptide 1 receptor agonists	
Weight loss	Beneficial weight loss has been observed with lixisenatide	

Introduction

Worldwide, the type 2 diabetes epidemic continues to expand and exert socioeconomic strain on national health care systems.¹ Statistics from the UK indicate that around 10% of National Health Service spending is on diabetes and its complications, which equates to £9 billion.² Although there is a wide variation in prevalence by European country, the total number of adults with diabetes in the region was predicted to reach 55.2 million by 2010, accounting for 8.5% of the adult population.³

In the UK, as in other countries, the prevalence of type 2 diabetes is increasing and varies with factors including age, ethnic group, and social deprivation. Quality and Outcomes Framework data, which provide information on people 17 years of age and older with type 2 diabetes registered with general practices, indicate that during the period April 2009 to March 2010, the number of people diagnosed in England increased by more than 125,000 on the previous year, resulting in a UK prevalence of 5.4%.⁴ The true prevalence will be far higher than this because this figure does not include the estimated 1.1 million people in the UK with undiagnosed type 2 diabetes. These disturbing figures illustrate the importance of preventing type 2 diabetes, and helping those who do have the disease to manage it to prevent serious complications, such as renal failure, diabetic retinopathy, amputation, and cardiovascular disease.

The past decade has seen considerable progress in our understanding of the pathogenetic mechanisms involved in the progression of the disease. The treatment of type 2 diabetes has taken advantage of these scientific advances and resulted in several new therapies coming to the market. Some of the most important developments in this area surround glucagon-like peptide 1 (GLP-1), a naturally occurring peptide that is released from the gut within minutes of eating a meal.⁵ GLP-1 possesses a number of properties that make it a potentially ideal antidiabetes agent, including glucose-dependent insulin secretion, inhibition of glucagon secretion, delayed gastric emptying, and promotion of satiety.

In addition, direct effects on beta-cell growth and survival have been identified.⁵

Two therapeutic strategies have been developed to take advantage of these actions. The first is to use GLP-1 receptor agonists, which have a substantially longer half-life than GLP-1 due to reduced degradation by the dipeptidyl peptidase 4 (DPP-4) enzyme. Exenatide and liraglutide are the two currently available GLP-1 receptor agonists. The second strategy is to inhibit DPP-4, which prolongs the half-life of endogenously released GLP-1 and has led to the development of the DPP-4 inhibitors. Both strategies have proved very successful and the use of these agents as add-on treatment for type 2 diabetes is endorsed by the National Institute for Health and Clinical Excellence,⁶ the European Association for the Study of Diabetes,⁷ and the American Diabetes Association,⁸ among others.

GLP-1 also has a number of favorable effects for patients with type 2 diabetes beyond its benefits on glucose control. For example, agents that activate the GLP-1 receptor improve glucose tolerance alongside a low risk of hypoglycemia, beneficial weight loss, and have the potential to modify disease progression.⁵ The diverse actions of this class, and their novel and complementary mechanism of action, make them an appealing addition to the current therapeutic options for treating type 2 diabetes and significant research is ongoing in this field. The latest agent to reach Phase III clinical trials is the GLP-1 receptor agonist, lixisenatide. To provide the most up to date information on this agent, the Clinicaltrials.gov registry was first searched to identify all relevant clinical trials, then conference abstracts, and Medline were searched to obtain all published articles. This review summarizes all the available published evidence for lixisenatide up to the end of June 2011.

Lixisenatide: a new GLP-1 receptor agonist

The very short half-life of endogenous GLP-1⁹ has led to extensive research to find new compounds with pharmacokinetic properties suitable for development of a

pharmaceutical agent. Exendin-4 was first isolated from the salivary gland of the Gila monster (*Heloderma suspectum*), and characterization showed that the peptide was structurally related to but distinct from GLP-1, with a sequence homology of 53%.⁹ Exendin-4 is a potent agonist for the mammalian GLP-1 receptor with a longer in vivo half-life, prolonged duration of action, and GLP-mimetic actions.

Lixisenatide (also known as AVE0010 and ZP10) is a GLP-1 receptor agonist in late-stage development. In 2003, Zealand Pharma outlicensed lixisenatide to Sanofi-Aventis who is now responsible for all further clinical development. Like exenatide, lixisenatide is a synthetic version of exendin-4. It is able to withstand physiological degradation by DPP-4 as a result of C-terminal modification with six lysine residues and deletion of one proline (Figure 1). The half-life of lixisenatide is 2–4 hours, and it is classed as a short-acting GLP-1-receptor agonist, compared with the long-acting GLP-1-based peptides, liraglutide and albiglutide. Despite its relatively short half-life, lixisenatide is intended for once-daily dosing as a result of its strong binding affinity to the GLP-1 receptor. Receptor binding studies have shown that the median inhibitory concentration (IC_{50}) of lixisenatide for the human GLP-1 receptor is 1.4 nM, which is approximately four-fold greater than the affinity of GLP-1.¹⁰ In contrast, liraglutide has been shown to displace radiolabeled GLP-1 from human GLP-1 receptors with an IC_{50} of 0.11 nM, compared with values of 0.35 nM for GLP-1 and 0.55 nM for exenatide.

Preclinical findings

The preclinical pharmacological profile of lixisenatide demonstrates a number of important acute and longer-term actions that are highly relevant to the maintenance of glucose homeostasis. A detailed review of the preclinical pharmacological profile of lixisenatide is provided by Werner et al¹¹ and is only briefly summarized here.

Effects on glucose-stimulated insulin secretion

The beneficial effects of lixisenatide on glycemic control have been demonstrated in both healthy animals and in

animal models of type 2 diabetes. In isolated pancreas from healthy Wistar rats, lixisenatide significantly improved glucose-stimulated insulin secretion compared with saline control after a switch to high glucose concentrations. The effect of lixisenatide on insulin secretion was greater than that observed with GLP-1, consistent with the greater affinity reported for lixisenatide at the GLP-1 receptor.¹²

When fed a lipid-rich diet, the inherited obesity gene mutation of the Zucker Diabetic Fatty (ZDF) rat provides us with an animal model that mimics human adult onset type 2 diabetes and its related complications. A continuous subcutaneous infusion of lixisenatide 50 µg/kg/day for 6 weeks to ZDF rats preserved both first-phase and second-phase glucose-stimulated insulin secretion and total insulin secretion, whereas untreated rats showed a progressive impairment of insulin secretion and loss of the biphasic pattern of insulin secretion during the development of type 2 diabetes.¹² Treated ZDF rats also demonstrated a suppression of glucagon secretion in response to high glucose concentrations.

Effects on blood glucose levels

In healthy normoglycemic dogs, single subcutaneous injections of lixisenatide produced dose-dependent reductions in plasma glucose after an oral glucose challenge and significantly reduced postprandial glucose excursions by 67% compared with placebo without increasing insulin concentrations.¹³ Using absorption of paracetamol as a measure of gastric emptying, the researchers observed that lixisenatide significantly reduced arterial plasma paracetamol concentration by 53% versus placebo, suggesting that the effect of lixisenatide on postprandial blood glucose excursions in dogs is, at least in part, related to inhibition of gastric emptying and delayed intestinal glucose absorption.¹³

Dose-dependent reductions in plasma glucose after an oral glucose challenge have been demonstrated in both the *db/db* mouse and ZDF rat,^{10,14} two rodent models of diabetes in which mutations in the leptin receptor gene result in obesity and insulin resistance. Importantly, this activity was glucose-dependent with no effect at physiological glucose concentrations. Although the lack of effective leptin signaling



Figure 1 Structure of lixisenatide. The amino acid sequence of lixisenatide is shown alongside that of exendin-4 and pharmacologically active forms of human glucagon-like peptide 1. Amino acids highlighted in black show elements of lixisenatide or exendin-4 that differ from human glucagon-like peptide 1. Amino acids highlighted in gray show elements unique to lixisenatide.¹¹

Abbreviation: GLP-1, glucagon-like peptide 1.

Note: Reprinted from *Regulatory Peptides*, Vol 164, U Werner, H Haschke, AW Herling, W Kramer, Pharmacological profile of lixisenatide: A new GLP-1 receptor agonist for the treatment of type 2 diabetes, Pages 58–64, Copyright 2010, with permission from Elsevier.

in *db/db* mice and ZDF rats promotes the development of diabetes via mechanisms that do not commonly occur in most human patients with type 2 diabetes, these animal models have contributed substantially to our understanding of the pathophysiology and treatment of type 2 diabetes and its complications. In *db/db* mice, chronic lixisenatide administration prevented the progressive deterioration in glucose tolerance observed in control animals and was associated with significant dose-dependent reductions in glycosylated hemoglobin (HbA_{1c}).¹⁰ In ZDF rats, a continuous subcutaneous infusion of lixisenatide 50 µg/kg/day for 12 weeks significantly decreased basal blood glucose and improved oral glucose tolerance compared with control animals.¹⁴ At the end of the study, there was also a significant 1.7% reduction in HbA_{1c} compared with controls. Lixisenatide had no hypoglycemic effect and did not change HbA_{1c} in normoglycemic rats.

Effects on beta cell function

There is also evidence from animal studies that lixisenatide can maintain beta cell mass and function through stimulation of islet cell proliferation and neogenesis, and inhibition of islet cell apoptosis. In two experiments in the *db/db* mouse model of diabetes in which animals were treated chronically with intraperitoneal administration of lixisenatide up to 500 µg/kg or control, lixisenatide preserved pancreatic insulin mRNA expression and was associated with a dose-dependent increase in beta cell mass.¹⁰

The effects of lixisenatide on beta cell function have also been evaluated using pancreatic islets isolated from eight post mortem subjects who did not have type 2 diabetes.¹⁵ The islets were cultured either acutely (1 hour) under physiological conditions at low (2.8 mmol/L) or high (20 mmol/L) glucose concentrations, or chronically (48 hours) under lipotoxic conditions, followed by a 1-hour incubation at low or high glucose concentrations. Under physiological conditions, lixisenatide dose-dependently increased glucose-stimulated insulin secretion in human islets to a greater degree than GLP-1. Chronic lipotoxic stress conditions led to increases in triglyceride content, decreases in insulin content, and reductions in glucose-stimulated insulin secretion in untreated human islets. Although lixisenatide and GLP-1 had no effect on triglyceride content, both peptides were able to prevent lipid-induced insulin depletion. Moreover, lixisenatide and GLP-1 were able to preserve the beta-cell response to glucose in human islets.

In vitro studies using the INS-1 rat pancreatic beta cell line have shown that lixisenatide protects beta cells against lipid-induced and cytokine-induced apoptosis in the order

of 50%–60%.¹⁶ Similar findings have been observed when beta cells are pretreated with several different rapid-acting or long-acting insulin analogs, and combined treatment of cells with lixisenatide and the long-acting analog, insulin glargine, has revealed additive activity and the prevention of both cytokine-induced and free fatty acid-induced apoptosis by up to 80%. These early findings are now being evaluated in clinical trials to determine whether the combination of a GLP-1 receptor agonist, such as lixisenatide, and insulin glargine might represent an effective strategy for preserving beta cell mass in patients with type 2 diabetes.

Pharmacokinetic and pharmacodynamic studies

Two lixisenatide trials have determined the dose-response effect and successfully demonstrated the restoration of insulin release in patients with type 2 diabetes taking oral anti-diabetes agents.^{17,18} In a 4-week study, the pharmacokinetics and pharmacodynamics of stepwise increasing doses of lixisenatide were examined in 64 patients with type 2 diabetes (HbA_{1c} ≥ 7.0% to ≤ 10.0%).¹⁷ Patients were randomized to one of three treatment arms, ie, lixisenatide once daily (5 µg in the morning with volume-matched placebo in the evening), lixisenatide twice daily (5 µg in the morning and 5 µg in the evening), or volume-matched placebo in the morning and evening. The lixisenatide treatment was increased, based on tolerability, every fifth day in increments of 2.5 µg to a maximum dose of 20 µg per injection (ie, 20 µg in the once-daily arm and 40 µg in the twice-daily arm). Patients were on a stable treatment with metformin and/or sulfonylurea, which was maintained throughout the study.

Lixisenatide concentrations increased in a dose-dependent manner, reaching peak concentrations between one and two hours (Table 1).¹⁷ At each dose level (5 µg, 10 µg, and 20 µg) the morning steady-state plasma concentration profiles were similar for the once-daily and twice-daily lixisenatide treatment groups. Mean area under the concentration-time curve (AUC) and peak plasma concentration (C_{max}) increased according to the dose and dose frequency of lixisenatide (Table 1). Comparisons of lixisenatide doses (5 µg, 10 µg, and 20 µg) demonstrated significantly greater AUC h.pg/mL values for the 20 µg group compared with all other treatment groups (Table 1).

At doses of 5–20 µg, both the once-daily and twice-daily lixisenatide treatment regimens were associated with statistically significant improvements in the primary endpoint of change in the AUC for postprandial blood glucose after a standardized test meal on day 28. The greatest reductions in postprandial blood glucose compared with placebo were seen

Table 1 Pharmacokinetic results from a study of 64 patients with type 2 diabetes randomized to lixisenatide once-daily or twice-daily, or placebo for 28 days. Results are for the 24-hour measurement period performed on days 4, 12, and 28¹⁷

Variable	Day 4 (5 µg)		Day 12 (10 µg)		Day 28 (20 µg)	
	Lixisenatide 1×/day (n = 8)	Lixisenatide 2×/day (n = 11)	Lixisenatide 1×/day (n = 9)	Lixisenatide 2×/day (n = 11)	Lixisenatide 1×/day (n = 9)	Lixisenatide 2×/day (n = 11)
AUC h·pg/mL (mean ± SD)	267.6 ± 130	512.6 ± 152	420.5 ± 178	916.0 ± 249	847.8 ± 337	1788.6 ± 709
C _{max} pg/mL (mean ± SD)	37.3 ± 12	50.9 ± 17	82.7 ± 37	108.6 ± 24	187.2 ± 70	234.4 ± 90
t _{max} h (median)	1.25	2.25	1.25	2.25	1.25	1.25
T _{1/2} h (median)	3.4	4.3	2.7	3.1	2.8	3.2

Abbreviations: AUC, area under the concentration-time curve; SD, standard deviation; t_{max}, time to peak plasma concentration; t_{1/2}, elimination half-life.

after the breakfast test meal; there were no significant differences between the two treatment regimens in the primary endpoint. As observed with other GLP-1 peptide agonists, five patients did form antibodies to lixisenatide, and pharmacokinetic data were reported only for those individuals who were antibody-negative (n = 59) due to a potential interaction between anti-lixisenatide antibodies and the assay to determine lixisenatide plasma concentrations. In this study, the half-life of lixisenatide was 2.7–4.3 hours and was slightly longer in the groups that received twice-daily dosing.

In a two-way crossover study, 22 patients with type 2 diabetes were randomized to a single subcutaneous injection of lixisenatide 20 µg or placebo.¹⁸ Two hours after the lixisenatide or placebo injection, patients received an intravenous bolus of glucose 0.3 g/kg body weight over a period of 30 seconds. Lixisenatide enhanced the first-phase insulin response to intravenous glucose by more than six-fold and second-phase insulin response by approximately three-fold compared with placebo (Figure 2). In this study,

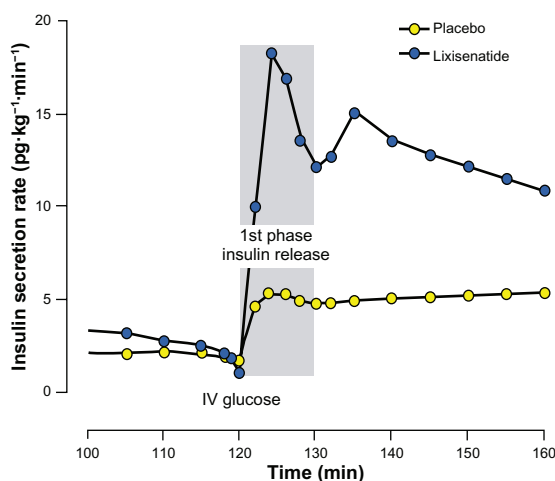


Figure 2 Mean insulin secretion rate after an intravenous glucose challenge following injection of lixisenatide 20 µg or placebo.¹⁸
Note: Data compiled from ClinicalTrials.gov.

lixisenatide did not affect glucagon suppression. Maximum plasma concentrations were achieved 2 hours after the single injection.

To determine the pharmacokinetics and safety of lixisenatide in patients with renal impairment, a single 5 µg subcutaneous injection was administered to eight healthy subjects with normal renal function (creatinine clearance >80 mL/minute), and eight each with mild (50–80 mL/minute), moderate (30–50 mL/minute), or severe renal impairment (<30 mL/minute, but not requiring dialysis).¹⁹ AUC and C_{max} values observed in patients with mild to moderate renal impairment did not differ significantly from those observed in healthy subjects. In patients with severe renal impairment, drug exposure was increased, suggesting that dosage adjustment may be required.

To characterize the dose-response effect of lixisenatide fully, a total of eight regimens (5, 10, 20, or 30 µg) each administered once daily or twice daily, were compared with placebo in a 13-week, randomized, placebo-controlled, parallel-group study of 542 patients with type 2 diabetes (HbA_{1c} ≥7.0% to <9.0%) who were inadequately controlled on metformin monotherapy.²⁰ The lixisenatide 20 µg and 30 µg doses were administered in escalating doses during the first 4 weeks of the study, with the dose initiated at 10 µg for 1 week and increased by 5 µg per week up to the target dose. At week 13, statistically significant reductions in the primary endpoint (change in HbA_{1c} from baseline to endpoint) were observed for all lixisenatide treatment groups compared with placebo (all *P* < 0.01 versus placebo). A dose-response relationship for HbA_{1c} level was observed for both the once-daily and twice-daily lixisenatide dosing regimens. Mean HbA_{1c} reductions from the mildly hyperglycemic baseline HbA_{1c} of 7.6% were 0.47%, 0.50%, 0.69%, and 0.76% for the once-daily lixisenatide regimens, and 0.65%, 0.78%, 0.75% and 0.87% for the twice-daily regimens, respectively, compared with 0.18% for placebo (Figure 3). A target

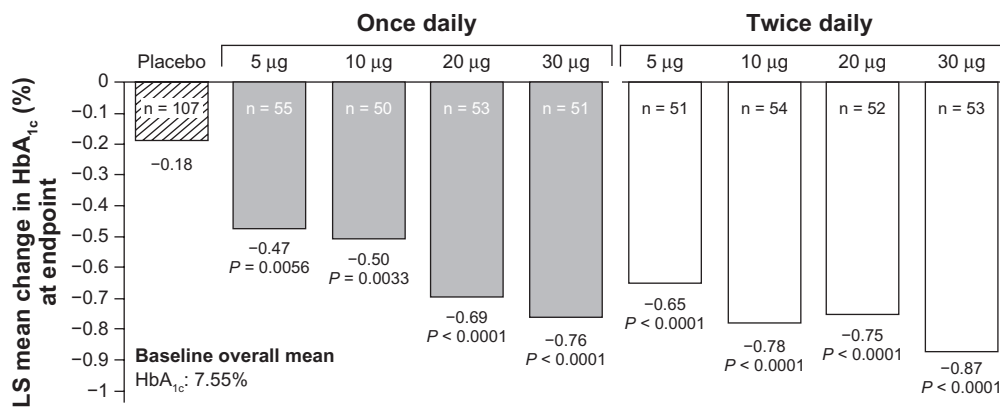


Figure 3 Least squares mean change in HbA_{1c} after 13 weeks of treatment with lixisenatide once-daily or twice-daily according to dosage and regimen.²⁰

Abbreviations: HbA_{1c}, glycosylated hemoglobin; LS, least squares.

Note: Reproduced from Becker RH, Ruus P, Liu Y-H, Kapitza C. Restoration of insulin release with lixisenatide in patients with type 2 diabetes. *Diabetologica*. 2010;53 Suppl 1:S339, with permission of the publisher.

HbA_{1c} of <7.0% at study end was achieved in 68% of patients receiving lixisenatide 20 µg and 30 µg once daily compared with 32% of patients receiving placebo ($P < 0.0001$). Statistically significant dose-dependent reductions from baseline in fasting and 2-hour postprandial plasma glucose were also observed. The improvements in glycemic control with lixisenatide were coupled with reductions in body weight, ie, 3.0 kg for lixisenatide 20 µg compared with 1.9 kg for placebo (Figure 4). In this study, the once-daily and twice-daily regimens provided similar levels of efficacy, and doubling the daily dose in the twice-daily regimens did not provide relevant additional improvements in glycemic control over the once-daily regimens.

Lixisenatide has also been investigated in a 4-week trial in 150 patients with type 2 diabetes not achieving adequate glycemic control with metformin, using liraglutide as the active comparator. The primary endpoint was change from

baseline in postprandial plasma glucose after a standardized breakfast. Although the trial has been completed, results have not yet been presented.

Efficacy studies: the GETGOAL program

The Phase III clinical trial program for lixisenatide began in 2008. Known as the GETGOAL program, it consisted of two parallel programs. The most advanced involved ten individual clinical trials to assess the efficacy and safety of lixisenatide in adult patients with type 2 diabetes treated with various oral antidiabetes agents or insulin. The program enrolled more than 4500 patients globally, the first results of which were presented in abstract form in 2010 (Table 2). The remaining trials are expected to complete in 2011. The second part of the program involved a combination of lixisenatide and the once-daily, long-acting insulin analog, insulin glargine.

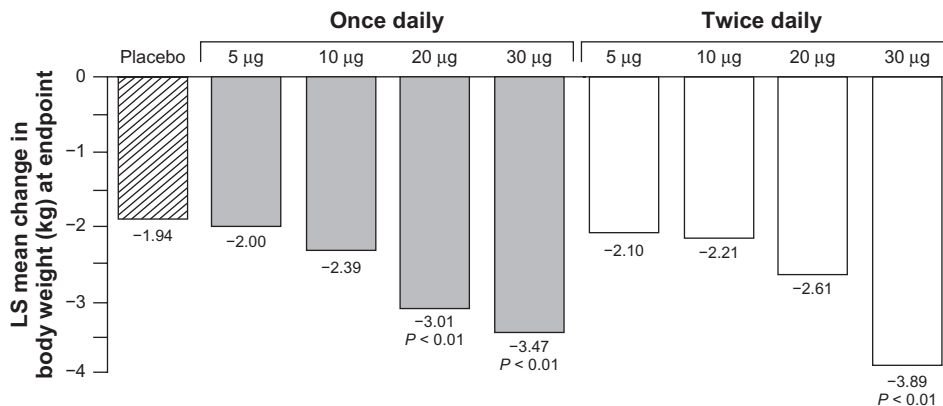


Figure 4 Least squares mean change in body weight after 13 weeks of treatment with lixisenatide once-daily or twice-daily according to dosage and regimen.²⁰

Note: Reproduced from Becker RH, Ruus P, Liu Y-H, Kapitza C. Restoration of insulin release with lixisenatide in patients with type 2 diabetes. *Diabetologica*. 2010;53 Suppl 1:S339, with permission of the publisher.

Abbreviation: LS, least squares.

Table 2 Summary of the GETGOAL Phase III clinical trial program with lixisenatide

Trial	Comparator	Participants	Duration (weeks)	Primary outcome	Secondary outcome	Status
GETGOAL-Mono	Lixisenatide vs PCB (1-step and 2-step titration)	361 adults previously untreated with antidiabetes agents	12	Change in HbA _{1c} from baseline	Changes in body weight, FPG, 2 hour-PPG	Completed
GETGOAL-FI	Lixisenatide + MET vs PCB + MET (1-step and 2-step titration)	450 adults previously treated with MET	24	Change in HbA _{1c} from baseline	Changes in body weight, FPG	Completed
GETGOAL-S	Lixisenatide + SU vs PCB + SU	859 adults previously treated with SU	24	Change in HbA _{1c} from baseline	Changes in body weight, FPG, 2 hour-PPG	Completed
GETGOAL-L	Lixisenatide + basal insulin vs PCB + basal insulin	495 adults previously treated with basal insulin	24	Change in HbA _{1c} from baseline	Changes in body weight, FPG, change from baseline in insulin doses	Completed
GETGOAL-P	Lixisenatide + PIO vs PCB + PIO	450 adults previously treated with PIO	24	Change in HbA _{1c} from baseline	Changes in body weight, FPG, fasting plasma insulin	Expected completion Q2 2011
GETGOAL-X	Lixisenatide + MET vs EXE + MET	634 adults previously treated with MET	24	Noninferiority in HbA _{1c} reduction from baseline	Changes in body weight, FPG, quality of life	Completed
GETGOAL-M	Lixisenatide (morning or evening dose) + MET vs PCB + MET	680 adults previously treated with MET	24	Change in HbA _{1c} from baseline	Changes in body weight, FPG, 2 hour-PPG	Completed
GETGOAL-Mono JAPAN LTS	Open-label lixisenatide (1- and 2-step titration)	66 adults not treated with antidiabetes agents	52	Safety measures	Changes in HbA _{1c} and FPG from baseline	Completed
GETGOAL-L-ASIA	Lixisenatide + basal insulin vs PCB + basal insulin	311 adults previously treated with basal insulin ± SU	24	Change in HbA _{1c} from baseline	Change from baseline in body weight, FPG, insulin doses	Completed
GETGOAL-M-As China	Lixisenatide + MET ± SU vs PCB + MET ± SU	380 adults previously treated with MET or MET + SU	24	Change in HbA _{1c} from baseline	Changes in body weight, FPG, 2 hour-PPG	Ongoing

Notes: All the 24-week GETGOAL trials with the exception of GETGOAL-L-ASIA have a variable extension period; the GETGOAL-Mono JAPAN LTS trial has a 24-week extension period. Data sourced from the ClinicalTrials.gov website (<http://clinicaltrials.gov/>).

Abbreviations: EXE, exenatide; MET, metformin; PCB, placebo; PIO, pioglitazone; SU, sulfonylurea; FPG, fasting plasma glucose; PPG, postprandial glucose.

For all these trials, the once-daily lixisenatide 20 µg dose was selected, because in previous trials it had demonstrated the best efficacy to tolerability ratio.

GETGOAL-Mono

The first results to be reported were those of the GETGOAL-Mono trial. In this 12-week trial, 361 patients with type 2 diabetes (HbA_{1c} 7%–10%) not currently receiving antidiabetes agents were randomized to one of four once-daily treatment regimens, ie, 119 patients underwent a one-step titration with lixisenatide (10 µg for 2 weeks then 20 µg), 120 underwent a two-step titration with lixisenatide (10 µg for 1 week, 15 µg for 1 week then 20 µg), 61 underwent a one-step placebo titration, and 61 underwent a two-step placebo titration.²¹ The mean age of patients was 54 years and the mean duration of type 2 diabetes was 2.5 years. Both lixisenatide titration groups were associated with statistically significant improvements in HbA_{1c} compared with placebo ($P < 0.0001$, Table 3). In addition, more patients in the lixisenatide groups achieved HbA_{1c} ≤6.5% (25.4% one-step titration, 31.9% two-step

titration) and <7.0% (46.5% one-step titration, 52.2% two-step titration) compared with placebo (26.8% and 12.5%, respectively; $P < 0.01$). Lixisenatide was associated with significant improvements in both 2-hour postprandial and fasting plasma glucose compared with placebo, with a particularly pronounced effect on postprandial plasma glucose (Table 3). Decreases in body weight were observed in all groups.

GETGOAL-X

Results from several other GETGOAL studies have been unveiled by Sanofi-Aventis and Zealand Pharma and presented in abstract form at conferences in 2011. GETGOAL-X was the first head-to-head trial comparing lixisenatide with another GLP-1 agonist. In this randomized, open-label, 24-week trial, once-daily lixisenatide 20 µg was compared with twice-daily exenatide 10 µg as add-on therapy in 634 people not achieving glycemic control with metformin ≥1.5 g/day.²² Both groups received a stepwise increase in dose, up to a maximum daily dose of 20 µg. The mean age of the patients was 57 years, mean duration of type 2 diabetes was 7 years,

Table 3 Mean baseline and 12-week changes in glycemic efficacy variables for 361 patients with type 2 diabetes randomized to one of four once-daily treatment regimens, ie, lixisenatide two-step titration (10 µg for 1 week, 15 µg for 1 week then 20 µg; n = 120), lixisenatide one-step titration (10 µg for 2 weeks then 20 µg; n = 119), placebo two-step titration (n = 61), or placebo one-step titration (n = 61)²¹

Variable		Placebo (n = 121)	Lixisenatide	
			2-step titration (n = 120)	1-step titration (n = 118)
HbA _{1c} (%)	Baseline	8.07 ± 0.92	7.97 ± 0.91	8.06 ± 0.85
	Change from baseline	-0.19 ± 0.12	-0.73 ± 0.12	-0.85 ± 0.12
	LS mean difference vs PCB	-	-0.54 ± 0.12	-0.66 ± 0.12
	95% CI	-	(-0.79 to -0.30)	(-0.90 to -0.42)
2-hour PPG (mmol/L)*	Baseline	13.99 ± 4.78	14.67 ± 3.78	14.55 ± 3.36
	Change from baseline	-0.65 ± 0.56	-4.51 ± 0.57	-5.47 ± 0.55
	LS mean difference vs PCB	-	-3.86 ± 0.77	-4.82 ± 0.74
	95% CI	-	(-5.38 to -2.35)	(-6.29 to -3.36)
Glucose excursion (mmol/L)*	Baseline	4.72 ± 3.65	5.45 ± 3.02	5.25 ± 2.89
	Change from baseline	-0.67 ± 0.45	-3.77 ± 0.45	-4.36 ± 0.44
	LS mean difference vs PCB	-	-3.10 ± 0.61	-3.69 ± 0.59
	95% CI	-	(-4.30 to -1.90)	(-4.85 to -2.53)
FPG (mmol/L)	Baseline	8.91 ± 2.17	9.17 ± 1.98	9.02 ± 1.97
	Change from baseline	+0.19 ± 0.26	-0.68 ± 0.25	-0.89 ± 0.25
	LS mean difference vs PCB	-	-0.87 ± 0.26	-1.08 ± 0.26
	95% CI	-	(-1.37 to -0.36)	(-1.59 to -0.58)

Notes: *At selected sites (n = 62, 60, and 65 for the placebo, lixisenatide 2-step, and lixisenatide 1-step groups, respectively); baseline data are mean ± standard deviation; change from baseline (to week 12 or last observation carried forward) data are LS mean ± standard error of the mean.

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; LS, least squares; PCB, placebo; PPG, postprandial plasma glucose.

and mean baseline HbA_{1c} was 8.0%. Lixisenatide achieved its primary endpoint of noninferiority in HbA_{1c} reduction from baseline compared with exenatide using a predefined upper limit of 95% confidence interval (CI) ≤0.4: least squares mean difference = 0.17 (95% CI 0.03–0.30, Table 4). Improvements in mean fasting plasma glucose and the percentage of patients achieving HbA_{1c} <7.0% were comparable between groups (Table 4). Mean body weight significantly

decreased from baseline, ie, 94.5 kg to 91.7 kg with lixisenatide and 96.7 kg to 92.9 kg with exenatide. Participants in this trial are also being followed in a variable extension of at least 52 weeks.

GETGOAL-S

GETGOAL-S was the largest trial in the clinical program and investigated the efficacy and safety of lixisenatide as add-on

Table 4 Preliminary results from the GETGOAL-X trial, a head-to-head comparison of lixisenatide and exenatide in patients not achieving adequate glycemic control with metformin ≥1.5 g/day²²

Parameter		Lixisenatide	Exenatide	
Mean baseline and 24-week changes in efficacy parameters (ITT population)		n = 311	n = 305	LS mean difference (95% CI)
HbA _{1c} (%)	Baseline ± SD	7.97 ± 0.82	7.96 ± 0.77	0.17 (0.03 to 0.30)
	LS mean ± SE change from baseline	-0.79 ± 0.05	-0.96 ± 0.05	
FPG (mg/dL)	Baseline ± SD	175 ± 37	174 ± 41	4.1 (-0.9 to 9.4)
	LS mean ± SE change from baseline	-22.0 ± 2.1	-26.1 ± 2.1	
Body weight (kg)	Baseline ± SD	94.5 ± 19.4	96.7 ± 22.8	1.02 (0.46 to 1.58)
	LS mean ± SE change from baseline	-2.96 ± 0.23	-3.98 ± 0.23	
Safety parameters (safety population)		n = 318	n = 316	P value
n (%) patients with symptomatic hypoglycemia*		8 (2.5%)	25 (7.9%)	<0.05
n hypoglycemic events		8	48	
n (%) patients with nausea		78 (24.5%)	111 (35.1%)	<0.05
n (%) patients with diarrhea		33 (10.4%)	42 (13.3%)	NS
n (%) patients with vomiting		32 (10.1%)	42 (13.3%)	NS

Note: *Event with clinical symptoms with either plasma glucose < 60 mg/dL (3.3 mmol/L) or prompt recovery after oral carbohydrate administration if no plasma glucose measurement was available.

Abbreviations: CI, confidence interval; HbA_{1c}, glycosylated hemoglobin; FPG, fasting plasma glucose; ITT, intent-to-treat; LS, least squares; NS, not significant; SD, standard deviation; SE, standard error of the mean.

therapy in patients not achieving glycemic control with a sulfonylurea, with or without metformin. GETGOAL-S was a randomized, double-blind, placebo-controlled study with a 24-week treatment period.²³ In total, 859 patients were randomized to receive either lixisenatide or placebo in stepwise increasing doses, up to a maintenance dose of 20 µg daily. The trial results have not yet been presented in abstract form, but a Sanofi-Aventis press release has reported that patients in the lixisenatide group experienced a significant reduction in HbA_{1c} levels, with a -0.74% difference versus placebo ($P < 0.0001$) at week 24. The drug was also associated with significant reductions in 2-hour postprandial ($P < 0.0001$) and fasting plasma glucose levels ($P < 0.0001$). Body weight was also significantly reduced ($P < 0.0001$) compared with patients receiving placebo.

Combined lixisenatide and insulin

In patients with type 2 diabetes, the progressive decline in beta cell function and increasing insulin resistance combined with an increased hepatic glucose output as a result of hypersecretion of glucagon leads to elevations in both fasting and postprandial glucose levels. Therefore, there is significant merit in the use of combination therapies to target these multiple pathophysiological defects. This has drawn attention to the possibility of using GLP-1 receptor agonists with basal insulin, the former agent targeting postprandial plasma glucose and the latter agent targeting fasting plasma glucose. Two trials in the GETGOAL program are evaluating this rationale.

GETGOAL-L-ASIA

GETGOAL-L-ASIA was the first study to evaluate lixisenatide in combination with a basal insulin. This 24-week, double-blind, placebo-controlled trial assessed the efficacy and safety of lixisenatide as add-on therapy in 311 Asian patients with type 2 diabetes not achieving glycemic control with basal insulin (with or without a sulfonylurea).²⁴ Patients in the trial had a mean type 2 diabetes duration of 14 years, mean age of 58 years, body mass index of 25.3 kg/m², and a mean baseline HbA_{1c} of 8.53%. Patients were randomized to add either lixisenatide 20 µg once daily ($n = 154$) or placebo ($n = 157$) to their existing treatment regimen; approximately 60% of patients were taking insulin glargine as their basal insulin. The primary endpoint was change in HbA_{1c} from baseline to week 24. Results from the trial showed that lixisenatide once daily in combination with basal insulin significantly improved glycemic control, the addition of lixisenatide to basal insulin reducing HbA_{1c}

levels by 0.9% versus placebo ($P < 0.0001$). Patients receiving lixisenatide were more likely to achieve an HbA_{1c} $\leq 6.5\%$ and $< 7.0\%$: 17.8% and 35.6% for lixisenatide, respectively, compared with 1.3% and 5.2%, respectively, for placebo ($P < 0.0001$). Lixisenatide was also associated with significantly greater improvements in 2-hour postprandial plasma glucose.

GETGOAL-L

The second trial to investigate the benefits of lixisenatide in combination with basal insulin was GETGOAL-L, which randomized 495 patients not achieving adequate glycemic control on a combination of insulin glargine and metformin to add-on lixisenatide 20 µg once daily or placebo for 24 weeks.²⁵ In the lixisenatide-basal insulin combination trials, the first step after screening was to optimize insulin therapy to the point where the patient was not achieving any further reductions in HbA_{1c} or where hypoglycemia became the limiting factor. The patients were then randomized to one of the two treatment arms while continuing with maximally optimized glargine therapy for a further 6 months, with both lixisenatide and insulin glargine injected in the morning within 1 hour prior to breakfast. The results are expected to be presented at a medical congress in 2011, but a Sanofi-Aventis press release has reported that the GETGOAL-L trial showed a significant reduction in HbA_{1c} levels ($P = 0.0002$) with lixisenatide, without a significant increase in the incidence of symptomatic hypoglycemia ($P = 0.14$) versus placebo. In addition, patients treated with lixisenatide had significantly improved postprandial plasma glucose after a test meal ($P < 0.0001$) and a significant reduction in body weight ($P < 0.0001$). These results confirm those of GETGOAL-L-Asia, this time in a broader population including both Caucasian and Asian patients.

Additional clinical efficacy trials Lixisenatide versus sitagliptin

In addition to the GETGOAL program, two other Phase III trials with lixisenatide were listed on the ClinicalTrials.gov registry. The first was a 24-week Phase III study comparing lixisenatide with sitagliptin as add-on therapy in 300 adults younger than 50 years of age, with a body mass index ≥ 30 kg/m² and not achieving adequate glycemic control with metformin. The primary outcome in this double-blind, double-dummy trial was the percentage of patients with HbA_{1c} values $< 7\%$ and a weight loss of at least 5% of baseline body weight. The trial has been completed, but results not yet presented.

Cardiovascular outcome trial

The second Phase III trial was ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 [lixisenatide]). This large cardiovascular outcome trial recruited patients with type 2 diabetes who had experienced an acute coronary syndrome event (ie, ST segment elevation myocardial infarction, non-ST segment elevation myocardial infarction, or unstable angina) with a target sample size of 6000. Patients were randomized to once-daily lixisenatide or placebo, with a median estimated follow-up period of approximately 2 years. The primary endpoint was time to the first occurrence of a primary cardiovascular event, ie, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina. This trial meets the new US Food and Drug Administration guidance introduced in 2008, which requires that manufacturers developing new drugs for type 2 diabetes provide evidence that the therapy will not increase the risk of cardiovascular events. Results from this trial are not expected until 2013.

Safety and tolerability

As a result of the lack of published data, safety and tolerability information on lixisenatide is currently limited, but the following information provides a summary of the published findings.

Treatment-emergent adverse events

In the GETGOAL-Mono trial there was only one (0.4%) serious treatment-emergent adverse event in a lixisenatide-treated patient (two-step titration group) compared with five (4.1%) in the placebo group.²¹ Nine patients discontinued due to a treatment-emergent adverse event, ie, five (4.2%) in the lixisenatide two-step group, three (2.5%) in the lixisenatide one-step group, and one (0.8%) in the placebo group.

In the GETGOAL-X trial, the proportion of patients with adverse events was generally comparable between the lixisenatide and exenatide groups.²² There were 33 (10.4%) patient discontinuations due to adverse events (mainly gastrointestinal) in the lixisenatide group and 41 (13.0%) with exenatide. A greater proportion of patients in the lixisenatide group tolerated the target dose of 20 µg/day (93% versus 83% with exenatide).

In GETGOAL-L-ASIA, 86% of patients on lixisenatide completed the trial compared with 92% of placebo patients.²⁴ Serious treatment-emergent adverse events occurred in 10 (6.5%) lixisenatide patients and nine (5.7%) placebo

patients. Fourteen (9.1%) patients in the lixisenatide group discontinued due to adverse events compared with five (3.2%) in the placebo group, mostly due to gastrointestinal events.

Gastrointestinal adverse events

The most frequent adverse events associated with lixisenatide include transient dose-dependent nausea, diarrhea, and vomiting.^{20–22,24} In the GETGOAL-Mono trial, nausea was the most frequent (24.2% for lixisenatide two-step, 20.2% for lixisenatide one-step, 4.1% for placebo).²¹ In the GETGOAL-X trial, overall gastrointestinal tolerability appeared better for lixisenatide versus exenatide, with fewer cases of nausea and vomiting (Table 4).²² In GETGOAL-L-ASIA, nausea and vomiting were reported in 39.6% and 18.2% of the patients, respectively, in the lixisenatide group and 4.5% and 1.9% of patients, respectively, in the placebo group.²⁴

Hypoglycemia

Similar to other GLP-1 agonists, lixisenatide only stimulates insulin secretion and suppresses glucagon secretion in the presence of elevated blood glucose and, as a result, the risk of hypoglycemia should be reduced compared with some other antidiabetes therapies. In the GETGOAL-Mono trial, symptomatic hypoglycemia occurred in three patients (2.5%) in the lixisenatide two-step group, one (0.8%) in the lixisenatide one-step group, and two (1.6%) in the placebo group, with no cases of severe hypoglycemia.²¹ In GETGOAL-X, initial results showed that significantly fewer people with type 2 diabetes treated with lixisenatide reported symptomatic hypoglycemia versus patients treated with exenatide, ie, eight (2.5%) versus 25 (7.9%), respectively; $P < 0.05$ (Table 4).²² A total of eight hypoglycemic events were reported in patients receiving lixisenatide compared with 48 events in patients receiving exenatide. No severe episodes were reported. With other GLP-1 agonists, the highest incidence of hypoglycemic events has been observed when they are used in combination with a sulfonylurea. Preliminary results from the GETGOAL-S trial report that lixisenatide as add-on therapy to a sulfonylurea did not significantly increase the risk of symptomatic hypoglycemia compared with placebo.²³ In the GETGOAL-L-ASIA trial, 42.9% of patients in the lixisenatide group reported symptomatic hypoglycemia compared with 23.6% in the placebo group.²⁴ However, in patients not receiving a sulfonylurea, the addition of lixisenatide to a basal insulin resulted in a hypoglycemia rate of 31.8% in lixisenatide patients and 28.3% in placebo patients. There were no cases of severe hypoglycemia.

Antibody formation

Antibody formation occurs in a significant number of patients treated with GLP-1 receptor agonists.²⁶ It is possible that exendin-4-based compounds, which include exenatide and lixisenatide, may result in greater antibody formation, possibly because of a lower homology with native GLP-1. However, only one study to date has reported antibody data with lixisenatide, and the relevance of antibody formation remains unclear.

Discussion

The clinical effectiveness of lixisenatide has been evaluated in the GETGOAL program. This was designed to assess the efficacy and safety of lixisenatide across the spectrum of type 2 diabetes care, both as monotherapy and in combination with commonly used antidiabetes agents, in a series of randomized, controlled trials in more than 4500 people (Table 2). The first Phase III results with lixisenatide have been presented and demonstrate that it exhibits the properties expected of a GLP-1 receptor agonist in terms of improving glycemic control while reducing or eliminating the risk of hypoglycemia and weight gain. If approved, lixisenatide would be the third GLP-1 receptor agonist to enter the market after exenatide and liraglutide, with which it would have to compete.

In a head-to-head trial, initial results showed noninferior HbA_{1c} reduction and weight loss with once-daily lixisenatide compared with twice-daily exenatide, whilst delivering a better safety and tolerability profile.²² However, in the Liraglutide Effect and Action in Diabetes (LEAD)-6 trial, a head-to-head comparison of subcutaneous liraglutide 1.8 mg once daily and exenatide 10 µg twice daily, liraglutide was associated with a significantly greater reduction in HbA_{1c} compared with exenatide (1.12% versus 0.79%, respectively).²⁷ It will not be known how lixisenatide compares with liraglutide until the results of the head-to-head trial with liraglutide become available. A key differentiating factor is likely to be the effect of lixisenatide on postprandial plasma glucose. Although liraglutide targets both fasting and postprandial plasma glucose, significantly greater reductions in fasting plasma glucose are achieved, reflecting the action of liraglutide as a 24-hour GLP-1 agonist. In contrast, lixisenatide achieves greater reductions in postprandial plasma glucose as a result of its more rapid time-action profile, while maintaining the ability to be dosed once daily.

The dosing regime is an important consideration for any new GLP-1 receptor agonist. With lixisenatide, dose-response relationships were demonstrated for both the once-daily and twice-daily regimens, with similar efficacy levels.²⁰ The once-daily 20 µg dose of lixisenatide demonstrated the best

efficacy-to-tolerability ratio and was selected for the GETGOAL program. The convenience of a once-daily dosing regimen is likely to be preferred by patients and would allow lixisenatide to compete with both twice-daily exenatide and once-daily liraglutide.

An important factor in the appeal of liraglutide and exenatide is the weight loss seen in many patients, and lixisenatide seems to produce similar results. The recent release of preliminary GETGOAL-S results, although not yet published in abstract form, indicate that lixisenatide as add-on to a sulfonylurea was associated with a significant decrease in body weight ($P < 0.0001$) compared with patients receiving placebo as add-on to a sulfonylurea.²³

A pronounced effect of lixisenatide on postprandial plasma glucose in addition to a tendency for weight loss has led to investigation of the combined effects of lixisenatide and long-acting insulins in patients with type 2 diabetes. There is a good rationale for such a combination, with one targeting postprandial and the other fasting plasma glucose, providing additive effects on HbA_{1c} and one associated with weight loss and the other with a degree of weight gain. In addition, both GLP-1 receptor agonists and insulin analogs, such as insulin glargine, exhibit a protective function on beta cells, suggesting that the two agents in combination might represent a new therapeutic option for preservation of beta cell mass in patients with type 2 diabetes. Recent results with exenatide have demonstrated the feasibility of such an approach. In a 30-week study, 261 adults with type 2 diabetes who were receiving insulin glargine alone or in combination with metformin and/or pioglitazone were randomized to exenatide or placebo while continuing to optimize their insulin treatment.²⁸ Patients had an average type 2 diabetes duration of 12 years, mean HbA_{1c} 8.3%–8.5%, and were receiving an average insulin dose of 47–50 U/day. At the end of the study, mean HbA_{1c} had decreased by 1.74% with exenatide and 1.04% with placebo (between-group difference, $-0.69%$ [95% CI, $-0.93%$ to $-0.46%$]; $P < 0.001$). The exenatide treatment group also experienced other benefits, including a weight decrease of 1.8 kg compared with a weight increase of 1.0 kg with placebo, and an average increase in insulin dose of 13 U/day with exenatide compared with 20 U/day for placebo. The estimated rate of minor hypoglycemia was similar between the groups.

The findings confirm the rationale for combining the complementary effects of a GLP-1 receptor agonist with a basal insulin and have paved the way for similar trials with lixisenatide. In addition, preclinical studies have shown that beta cells treated with a combination of lixisenatide and

insulin glargine are protected against cytokine-induced and free fatty acid-induced apoptosis, with additive benefits for the two agents in combination compared with either alone.¹⁶ The findings suggest that a combination of a GLP-1 receptor agonist and insulin glargine might represent an effective strategy for preserving beta cell mass in patients with type 2 diabetes and potentially could alter disease progression. Phase III clinical trials for the lixisenatide and insulin glargine combination have been completed, with preliminary results showing an approximately 0.9% reduction in HbA_{1c} on top of basal insulin.^{24,25}

The currently available data show that lixisenatide is well tolerated. The GLP-1 receptor represents an established therapeutic target in type 2 diabetes, with agonists of this receptor demonstrating improved glucose tolerance alongside a low risk of hypoglycemia, beneficial weight loss, and the potential to modify disease progression. Early results with lixisenatide look promising, but data from the GETGOAL program are only just beginning to appear, and before any firm conclusions can be made, must be published in peer-reviewed journals. If results are positive, lixisenatide will be the third GLP-1 receptor agonist to enter the market. The factor that may distinguish it from exenatide and liraglutide is its strong postprandial effect. This property may prove beneficial in patients with mildly elevated HbA_{1c}, in whom a therapeutic response is difficult to achieve with many existing antidiabetes therapies, as well as for use in combination with a basal insulin, such as insulin glargine, to achieve better glycemic control and minimize weight gain.

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